Departement für Pferde, Abteilung Anästhesiologie
der Vetsuisse-Fakultät Universität Zürich

Direktor: Prof. Dr. med. vet. Anton Fürst

Arbeit unter wissenschaftlicher Betreuung von
Frau PD Dr. med. vet. Martina Mosing

Comparison of the effects of propofol or alfaxalone for anaesthesia induction and maintenance on respiration in cats

Inaugural-Dissertation

zur Erlangung der Doktorwürde der
Vetsuisse-Fakultät Universität Zürich

vorgelegt von

Ivo Ulisse Campagna

Tierarzt
von Chironico, Tessin

genehmigt auf Antrag von

Prof. Dr. med. vet. PhD Regula Bettschart-Wolfensberger, Referentin

2015

Inhaltsverzeichnis

Vetsuisse-Fakultät Universität Zürich (2015)

Ivo Ulisse Campagna

Abteilung Anästhesiologie
Vetsuisse-Fakultät Universität Zürich
gschmid@vetclinics.uzh.ch

Comparison of the effects of propofol or alfaxalone for anaesthesia induction and maintenance on respiration in cats

Blinded, randomized, prospective clinical trial.
20 cats undergoing ovariohysterectomy were enrolled.
After premedication with medetomidine and meloxicam, the cats were randomly assigned into two groups: group A (n = 10) receiving alfaxalone 5 mg/kg/minute followed by 10 mg/kg/hour intravenously (IV) and group P (n = 10) receiving propofol 6 mg/kg/minute followed by 12 mg/kg/hour IV for induction and maintenance of anaesthesia, respectively. After endotracheal intubation, the tube was connected to a non-rebreathing system delivering oxygen 100%. The anaesthetic maintenance drug rate was adjusted (± 0.5 mg/kg/hour) every 5 minutes according to a scoring sheet based on physiologic variables and clinical signs. If apnoea > 30 seconds, end-tidal carbon dioxide (PE'CO2) > 7.3 kPa or arterial haemoglobin oxygen saturation (SpO2) < 90% occurred, manual ventilation was provided. Methadone was administered postoperatively.
Manual ventilation was required in 2 and 8 of the cats in group A and P ($p = 0.02$). Two vs 2, 0 vs 4 and 0 vs 6 cats in group A vs P showed apnoea ($p = 1$), PE'CO2 > 7.3 kPa ($p = 0.08$) or SpO2 < 90% ($p = 0.01$).
Alfaxalone might be better than propofol for induction and maintenance of anaesthesia when artificial ventilation cannot be provided.

Keywords: feline, ventilation, respiration, continuous rate infusion, total intravenous anaesthesia

Vetsuisse-Fakultät Universität Zürich (2015)

Ivo Ulisse Campagna

Abteilung Anästhesiologie
Vetsuisse-Fakultät Universität Zürich
gschmid@vetclinics.uzh.ch

Comparison of the effects of propofol or alfaxalone for anaesthesia induction and maintenance on respiration in cats

Zusammenfassung:

Vergleich der Wirkungen von Propofol oder Alfaxalon zur Anästhesieeinleitung und Erhaltung auf die Atmung bei Katzen

Verblindete, randomisierte, prospektive klinische Studie.
20 Katzen bei denen eine Ovariohysterektomie geplant war wurden einbezogen.
Nach Prämedikation mit Medetomidin und Meloxicam wurden die Katzen zufällig zwei Gruppen zugeordnet: Gruppe A (n = 10), Alfaxalon 5 mg/kg/Minute, gefolgt von 10 mg/kg/Stunde intravenös (IV) und Gruppe P (n = 10) Propofol 6 mg/kg/Minute, gefolgt von 12 mg/kg/Stunde IV für die Induktion und Aufrechterhaltung der Anästhesie. Nach Intubation wurde der Tubus mit einem Nicht-Rückatemsystem, welches Sauerstoff 100% lieferte, verbunden. Die Dosierung des jeweiligen Anästhetikums wurde alle 5 Minuten gemäss einem Bewertungsbogen geändert. Dieser basierte auf den physiologischen Variablen sowie klinischen Anzeichen der Anästhesietiefe (± 0,5 mg/kg/Stunde). Wenn Apnoe > 30 Sekunden, endexspiratorisches Kohlendioxid (PE'CO2) > 7.3 kPa oder arterielle Hämoglobin-Sauerstoffsättigung (SpO2) < 90 % auftraten, wurden die Tiere manuell beatmet. Methadon wurde postoperativ verabreicht.
Manuelle Beatmung war bei 2 und 8 der Katzen in Gruppe A und P erforderlich (p = 0,02). Zwei vs 2, 0 vs 4 und 0 vs 6 Katzen in Gruppe A vs P zeigten Apnoe (p = 1), PE'CO2> 7.3 kPa (p = 0.08) oder SpO2 < 90 % (p = 0.01).
Alfaxalon könnte besser als Propofol sein für die Induktion und Aufrechterhaltung von Anästhesien falls eine künstliche Beatmung nicht bereit gestellt werden kann.

Schlagwörter: Katzen, Beatmung, Atmung, kontinuierliche Infusion, totale intravenöse Anästhesie

Veterinary Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2014 doi:10.1111/vaa.12231

RESEARCH PAPER

Comparison of the effects of propofol or alfaxalone for anaesthesia induction and maintenance on respiration in cats

Ivo Campagna*, Andrea Schwarz*, Stefanie Keller†, Regula Bettschart-Wolfensberger* & Martina Mosing*
*Division of Anaesthesiology, Equine Department, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland
†Section of Small Animal Reproduction, Clinic of Reproductive Medicine, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

Correspondence: Ivo Campagna, Division of Anaesthesiology, Equine Department, Vetsuisse Faculty, University of Zurich, Winterthurerstrasse 260, 8057 Zurich, Switzerland. E-mail: icampagna@vetclinics.uzh.ch

Abstract

Objective To compare the effects of propofol and alfaxalone on respiration in cats.

Study design Randomized, 'blinded', prospective clinical trial.

Animals Twenty cats undergoing ovariohysterectomy.

Methods After premedication with medetomidine 0.01 mg kg^{-1} intramuscularly and meloxicam 0.3 mg kg^{-1} subcutaneously, the cats were assigned randomly into two groups: group A (n = 10) were administered alfaxalone 5 mg kg^{-1} $minute^{-1}$ followed by 10 mg kg^{-1} $hour^{-1}$ intravenously (IV) and group P (n = 10) were administered propofol 6 mg kg^{-1} $minute^{-1}$ followed by 12 mg kg^{-1} $hour^{-1}$ IV for induction and maintenance of anaesthesia, respectively. After endotracheal intubation, the tube was connected to a non-rebreathing system delivering 100% oxygen. The anaesthetic maintenance drug rate was adjusted (± 0.5 mg kg^{-1} $hour^{-1}$) every 5 minutes according to a scoring sheet based on physiologic variables and clinical signs. If apnoea > 30 seconds, end-tidal carbon dioxide ($P_E'CO_2$) > 7.3 kPa (55 mmHg) or arterial haemoglobin oxygen saturation (SpO_2) < 90% occurred, manual ventilation was provided. Methadone was administered postoperatively. Data were analyzed using independent-samples t-tests, Fisher's exact test, linear mixed-effects models and binomial test.

Results Manual ventilation was required in two and eight of the cats in group A and P, respectively (p = 0.02). Two cats in both groups showed apnoea. $P_E'CO_2$ > 7.3 kPa was recorded in zero *versus* four and SpO_2 < 90% in zero *versus* six cats in groups A and P respectively. Induction and maintenance dose rates (mean ± SD) were 11.6 ± 0.3 mg kg^{-1} and 10.7 ± 0.8 mg kg^{-1} $hour^{-1}$ for alfaxalone and 11.7 ± 2.7 mg kg^{-1} and 12.4 ± 0.5 mg kg^{-1} $hour^{-1}$ for propofol.

Conclusion and clinical relevance Alfaxalone had less adverse influence on respiration than propofol in cats premedicated with medetomidine. Alfaxalone might be better than propofol for induction and maintenance of anaesthesia when artificial ventilation cannot be provided.

Keywords continuous rate infusion, feline, respiration, total intravenous anaesthesia, ventilation.

Introduction

Total intravenous anaesthesia (TIVA) is an alternative to inhalation anaesthesia for maintenance of

general anaesthesia. One advantage of TIVA, by using continuous rate infusion (CRI), is a more stable plasma level of the anaesthetic compared to repeated boli. This may result in a constant level of anaesthesia by adjusting the infusion rate of the injectable anaesthetic to the perceived level of anaesthesia, compared to the oscillating effect of repeated boli administration (White 1983).

Alfaxalone and propofol, two injectable anaesthetics, are suitable for CRI because they have a rapid onset, short duration of action, fast redistribution and short elimination half-life (Morgan & Legge 1989; Whittem et al. 2008). Depth of anaesthesia can be adjusted quickly by changing the rate of infusion, in contrast to other injectable anaesthetics such as ketamine.

Alfaxalone and propofol have both been used for induction and maintenance of anaesthesia in cats (Andress et al. 1995; Liehmann et al. 2006; Muir et al. 2009; Beths et al. 2014), but no direct comparison of the two drugs can be found in the literature. The main difference between these agents seems to be the effect on respiration. While respiratory depression and apnoea have been identified during propofol anaesthesia (Liehmann et al. 2006) cats did not exhibit apnoea or a decrease in arterial haemoglobin oxygen saturation (SpO_2) < 90% during induction and maintenance of anaesthesia using alfaxalone (Schwarz et al. 2014).

The primary reason for the present study was our clinical observation that cats appeared to show less apnoea when alfaxalone was used for induction and maintenance of anaesthesia compared to propofol.

The hypothesis of this study was that cats anaesthetized with a CRI of alfaxalone would develop less apnoea (>30 seconds), hypercapnia (>7.3 kPa; 55 mmHg) or hypoxemia (SpO_2 < 90%) and require less ventilatory support compared to cats anaesthetized with a CRI of propofol.

Materials and methods

The present study was approved by the Committee for Animal Experimentation of the Canton Zurich, Switzerland (Nr. 164/ November 9th 2011).

Animals

Twenty female cats scheduled for elective ovariohysterectomy were enrolled in the study with informed owner consent. All cats underwent a clinical examination and were deemed to be in good health. Exclusion criteria were age <5 months, American Society of Anesthesiologists (ASA) classification > II, obvious pregnancy or lactation.

Preanaesthetic preparation and anaesthesia

Cats were housed in the hospital for 24 hours prior to anaesthesia. Food was withheld overnight, but water was available until premedication was administered.

Premedication consisted of medetomidine 0.01 mg kg^{-1} intramuscularly (IM) (Dorbene; Graeub AG, Switzerland) and meloxicam 0.3 mg kg^{-1} subcutaneously (SC) (Metacam; Boehringer Ingelheim, Switzerland). Fifteen minutes after premedication, a 22 gauge catheter (Terumo Surflo; Provet AG, Switzerland) was placed in the left or right cephalic vein and a lactated Ringer's infusion (Ringer-Lactate; Fresenius Kabi AG, Switzerland) was started at a constant rate of 10 mL kg^{-1} $hour^{-1}$. Cefazoline 22 mg kg^{-1} (Kefzol; Teva Pharma AG, Switzerland) was administered intravenously (IV). Before induction, sedation was scored using a numeric rating scale with 0) able to stand and walk; 1) able to lie sternal; 2) able to lift the head; 3) able to raise the head when hands clapping; 4) not able to lift the head, unresponsive, lies quietly.

After rating the sedation, cats were allocated to one of two anaesthetic techniques in a randomised fashion using a computer program (R 3.0.1; GNU Software Foundation, Switzerland). Anaesthesia was induced 25 minutes after premedication.

Group A received a CRI of alfaxalone 5 mg kg^{-1} $minute^{-1}$ (Alfaxan; Vétoquinol AG, Switzerland) for induction until intubation criteria described below were reached. The maintenance dose of alfaxalone was 10 mg kg^{-1} $hour^{-1}$. Similarly, group P received propofol 6 mg kg^{-1} $minute^{-1}$ for induction (Propofol 1%; Fresenius Kabi AG) followed by 12 mg kg^{-1} $hour^{-1}$ for maintenance. Both drugs were administered IV using a syringe driver (Syramed µSP6000; Arcomed, Switzerland).

During induction, depth of anaesthesia was assessed in all cats using a modified predescribed intubation score (Martinez Taboada & Murison 2010. Once the eye had rotated ventromedially, the palpebral reflex and jaw tone were checked and if absent lidocaine (Lidocain 20 mg mL^{-1}; Kantonsapotheke, Switzerland) was sprayed on the larynx (2 mg $spray^{-1}$, one or two sprays at the back of the throat). Thereafter, an attempt to

intubate the trachea with a cuffed endotracheal tube was performed every 10–15 seconds. The same experienced anaesthetist (MM) was responsible for tracheal intubation and was unaware of the treatment (syringes and infusion lines blacked out and a second person controlling pumps and recording values). As soon as the endotracheal tube passed through the larynx, the syringe driver was immediately stopped and the drug amount recorded. The infusion pump settings were changed to the maintenance dose and restarted. The cats were placed in dorsal recumbency, the endotracheal tube was connected to a non-rebreathing system (Mapleson D, Infant T-piece system; Intersurgical Ltd., UK) delivering a fixed fraction of inspired oxygen of 1.0 with a flow rate of 300 mL kg^{-1} $minute^{-1}$. Baseline values (T0) were recorded.

In all cats, depth of anaesthesia was evaluated by one experienced anaesthetist, who adjusted the continuous infusion rate every 5 minutes according to a predefined cardiovascular scoring sheet (Appendix S1) including pulse rate (PR) and mean arterial pressure (MAP) but also clinical signs (palpebral reflex, jaw tone, globe position). If movement or swallowing occurred, an additional bolus of either alfaxalone 0.5 mg kg^{-1} (group A) or propofol 0.5 mg kg^{-1} (group P) was administered IV. When respiratory rate (f_R) exceeded 40 breaths $minute^{-1}$, a bolus of 0.25 mg kg^{-1} of either alfaxalone or propofol was administered IV. In both cases the bolus was administered using the syringe driver, which determined the speed of injection (0.16 mL $second^{-1}$).

The cats were kept warm using a warm-water blanket (Hico-Aquatherm 660; Nufer Medical, Switzerland) and a forced-air warming system (Bair Hugger 505; Augustine Medical, Deutschland).

Monitoring and data collection

During anaesthesia, the following variables were recorded every 5 minutes, using a multi-parameter monitor (Carescape Monitor B850; GE Medical Systems, PA, USA): PR from the pulse oximeter, f_R, SpO_2, oesophageal temperature (T), end-tidal carbon dioxide ($P_E'CO_2$) measured with the previously calibrated sidestream capnograph (sampling rate: 200 mL $minute^{-1}$ ± 20 mL).

An additional pulse oximeter (Ohmeda TruSat; Datex Ohmeda Inc., PA, USA) was used to monitor PR and SpO_2 in real time and to countercheck the reciprocal pulse oximetry reading in case of loss of signal of one device. Both pulse oximeter probes were placed on the tongue.

Mean arterial pressure was measured oscillometrically every 5 minutes (HDO; S+B MedVET GmbH, Germany) with the cuff size selected according to the manufacturer's instructions (cuff size c1 was chosen for all cats), placed on the root of the tail. In case of artefacts (recognized by real-time observation of blood pressure) the measurement was immediately repeated. If MAP decreased to <55 mmHg, a bolus of 3 mL kg^{-1} hetastarch (HAES steril 10%; Fresenius Kabi AG) was administered IV over 15 minutes. If the MAP did not responded to hetastarch therapy within 10 minutes, a CRI of dobutamine 1 µg kg^{-1} $minute^{-1}$ IV (Dobutamin Liquid; Fresenius Kabi AG) was started.

Manual ventilation was instituted when apnoea (defined as the absence of respiratory movements of the thorax) persisted >30 seconds or the SpO_2 was <90% (on both pulse oximeters), and f_R was adjusted to maintain $P_E'CO_2$ between 6.6 and 7.5 kPa (50–55 mmHg). The event was recorded. If spontaneous respiratory movements reappeared between manual breaths and/or SpO_2 increased to >90% within 5 minutes the cats were allowed to breathe spontaneously. If cats did not show any spontaneous respiratory movements within the 5 minute time period, they were excluded from further data collection. Hypercapnia was defined as $P_E'CO_2$ > 7.5 kPa (55 mmHg) and the occurrence, during spontaneous ventilation, was recorded and compared between groups.

Venous blood samples were collected anaerobically from the jugular vein for blood gas analysis (i-STAT1 Analyzer; Abbott, NJ, USA) and haemoglobin (Hb) measurements (HemoCue Hb 201^+; HEMOCUE AB, Sweden) immediately after intubation, 30 and 60 minutes after induction and were analysed immediately.

Ovariohysterectomy was performed by the same surgeon in all cats. In order to be able to confirm an adequate and comparable level of anaesthesia in both groups PR, f_R, $P_E'CO_2$ and SpO_2 were recorded electronically every 10 seconds, beginning 1 minute before until 1 minute after specific surgical events (SE). The values before and after SE were compared retrospectively. The following SE were predefined: securing of drapes with Backhaus clamps (SEdrape), first incision (SEcut), ligation of the two ovarian pedicles and cervix (SEovar1, SEovar2 and SEcervix) first suture of the fascia (SEfascia), subcutis

(SEsubcutis) and cutis (SEfirst cutis), and the last cutis suture (SElast cutis).

Sixty minutes after intubation, or at the end of the surgical procedure, anaesthetic infusions were discontinued and the total amount of agent administered was recorded. The duration of anaesthesia was from the time of intubation to the time of stopping the syringe driver.

Recovery from anaesthesia

The trachea was extubated when a brisk palpebral reflex or ear movement was observed. The time from CRI termination to the first controlled attempt to lift the head and first sternal position was recorded. The presence of opisthotonus or myoclonus for more than 5 seconds was recorded. All cats were administered methadone 0.1 mg kg^{-1} IM (Methadone Streuli; Streuli Pharma SA, Switzerland), immediately after extubation.

Statistical analysis

A priori, a power calculation was performed using online software (G*Power, Version 3.0.10, Erdfelder, Faul and Buchner 1996; www.gpower.hhu.de) for the primary outcome measure, occurrence of apnoea between group A and group P, using Fisher's exact test with a power of 0.8 (1-β error). The difference of estimated mean values between the groups was based on preliminary (Schwarz et al. 2014) and internal clinical audit data (occurrence of apnoea group A = 20%; group P = 80%). It was anticipated that a significant difference of 0.05 (α error) between treatments could be detected in two groups of ten cats. Statistical data analysis was performed using commercially available software (Microsoft Excel 2003 for Windows; Microsoft Corporation, Washington, USA; SPSS Version 21 for Windows; IBM Corporation, WA, USA and R Version 3.0.1; GNU Software Foundation with the package nlme 3.1-110 2013, Zurich, Switzerland). Differences between groups regarding age, body mass, sedation score, anaesthesia duration, amount of received boli and recovery times were compared using independent-samples *t*-tests. Occurrence of apnoea, SpO_2 < 90%, $P_E'CO_2$ > 7.5 kPa (55 mmHg) and opisthotonus/myoclonus in the two groups was compared using Fisher's exact test.

For the outcome variables PR, f_R, SpO_2, MAP, $P_E'CO_2$, T, pH, partial pressure of carbon dioxide in venous blood ($PvCO_2$), bicarbonate (HCO_3), and Hb. Potential group and time effect were assessed using linear mixed-effects models to consider potential clustering within animals. Model selection was based on AIC (Akaike information criteria) with lower AIC values indicating a better model fit. For all analyses, $p \leq 0.05$ was considered statistically significant. Differences regarding PR, f_R, $P_E'CO_2$ and SpO_2 before and after the different surgical events (SE) were examined with a significant value set at $p \leq 0.2$ for clinical relevance. These data were than analysed between groups using Binomial test and confidential intervals of 95% were compared. Values are reported as mean ± SD for descriptive statistics.

Results

Animals

Data from all 20 cats enrolled in the present study were analysed (Fig. 1). There were no statistically significant differences between groups regarding age: 1.0 ± 0.6 years (group A) *versus* 1.1 ± 1.1 years (group P), weight: 3.1 ± 0.7 kg (group A) *versus* 2.8 ± 0.6 kg (group P), sedation score: 2 ± 2 (group A) *versus* 2 ± 1 (group P) and anaesthesia duration: 74 ± 11 minutes (group A) *versus* 74 ± 10 minutes (group P).

Induction and maintenance of anaesthesia

The mean ± SD anaesthesia induction doses were 11.6 ± 0.3 and 11.7 ± 2.7 mg kg^{-1} and maintenance dose was 10.7 ± 0.8 and 12.4 ± 0.5 mg kg^{-1} $hour^{-1}$ for alfaxalone and propofol, respectively. Cats received 3 ± 3 boli of 0.5 mg kg^{-1} (in case of movement or swallowing) in group A and 2 ± 3 boli in group P during the procedure ($p = 0.88$). Two cats in each group required ≥6 boli: 7 and 8 (group A), 6 and 9 (group P). All other cats received ≤3 boli (five and three cats in group A and P, respectively). All cats had a f_R < 40 breaths $minute^{-1}$, therefore no cat received the 0.25 mg kg^{-1} bolus.

Gas exchange and ventilation

Two cats in group A and eight in group P needed manual ventilatory support for <5 minutes ($p = 0.02$) (Table 1). No cat in group A *versus* six cats in group P showed a SpO_2 < 90% after induction (T0) ($p = 0.01$). The SpO_2 did not decrease

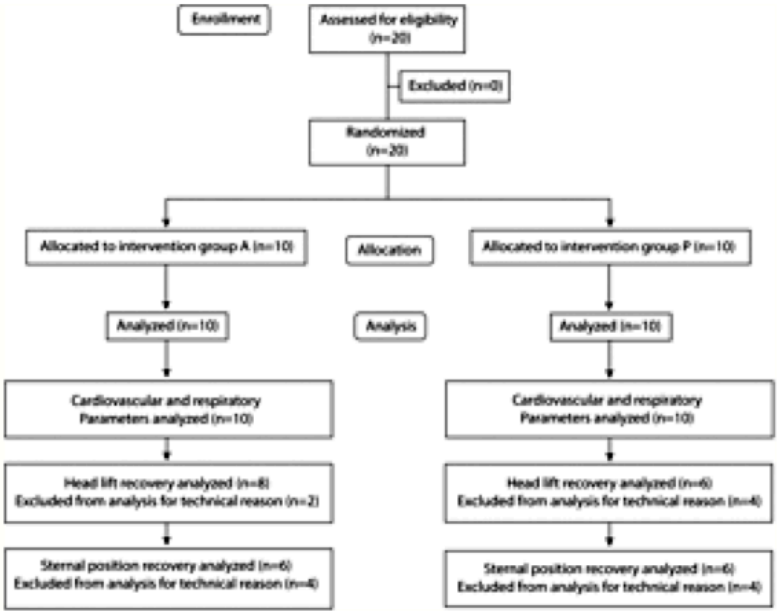

Figure 1 CONSORT Diagram. Technical difficulties included problems and interference with the video recording of the recovery.

Table 1 Occurrence of apnoea (no chest movement for more than 30 seconds), arterial haemoglobin oxygen saturation (SpO_2) < 90% and end-tidal carbon dioxide ($P_E'CO_2$) > 7.3 kPa (55 mmHg) in 20 cats anaesthetized with alfaxalone (group A) or propofol (group P) continuous rate infusion, after premedication with medetomidine and meloxicam

	Variables			
	Apnoea	$P_E'CO_2$ > 7.3 kPa	SpO_2 < 90%	Ventilatory support
Group A (n = 10)	2	0	0*	2*
Group P (n = 10)	2	4	6	8

*Significant difference between groups ($p < 0.05$).

<90% in any cat at any other time point. No cat in group A experienced hypercapnia ($P_E'CO_2$ > 7.5 kPa) during anaesthesia while four cats in group P did ($p = 0.08$). End-tidal CO_2 was significantly higher in group P over time ($p = 0.02$) (Fig. 2a).

In both groups respiratory rate increased initially and then decreased linearly after 30 minutes in group A and 50 minutes in group P (Fig. 2b). No difference was observed between groups. No difference was observed between groups for SpO_2 over time.

Cardiovascular variables and temperature

Pulse rate increased over time in both groups ($p < 0.0001$), but no difference was observed between groups (Fig. 2c). No arrhythmias were observed in any cat. Mean arterial pressure (Fig. 2d) was significantly higher in group P over time ($p = 0.03$). No hypotension was detected in any cat. No cat required hetastarch or dobutamine. Oesophageal temperature decreased in both groups over time ($p < 0.0001$), but no difference was found between groups.

Physiologic variables at surgical events

No significant differences were observed within group A and P regarding PR, f_R, $P_E'CO_2$ and SpO_2 before and after the nine predefined surgical events.

Venous blood-gas analysis

The pH (Fig 3a) was lower ($p < 0.001$) while HCO_3 was higher in group P ($p = 0.05$) at the three measurement points. No difference was observed for P_VCO_2 (Fig 3b) and base excess (BE). The Hb was lower directly and 30 minutes after induction in group A ($p = 0.04$).

Recovery times and quality

The time until head lift was evaluated in eight and six cats and the time until sternal recumbency in

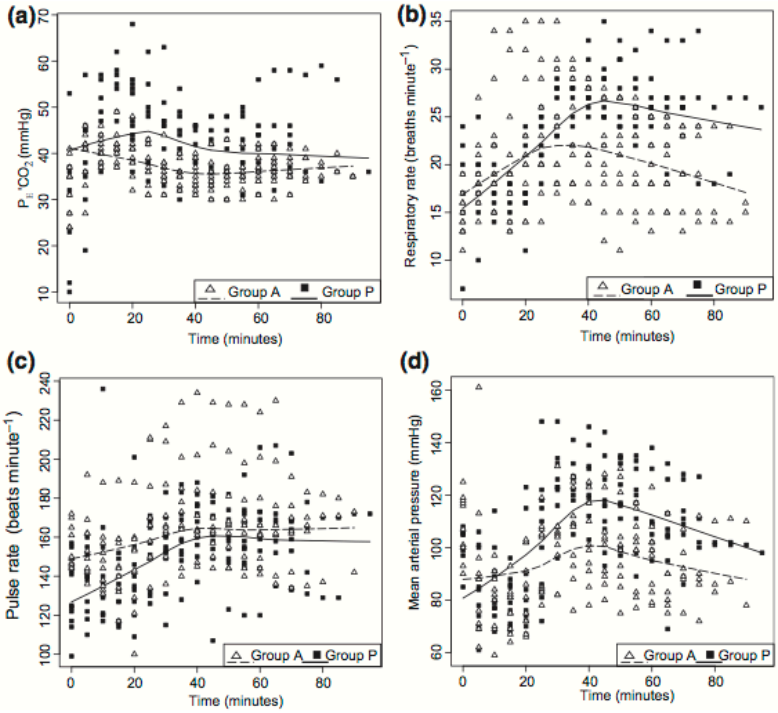

Figure 2 (a) Mean end-tidal carbon dioxide ($P_{E'}CO_2$; mmHg), (b) mean respiratory rate (f_R; breaths minute^{-1}), (c) mean pulse rate (PR; beats minute^{-1}), (d) mean of the mean arterial pressure (MAP; mmHg) over time in 20 cats under alfaxalone (group A) or propofol (group P) continuous rate infusion, premedicated with medetomidine and meloxicam.

eight and six cats in group A and P, respectively. No significant difference was observed in recovery times between the groups as reported in Table 2. Two cats in each group showed myoclonus or opisthotonus which resolved without therapy. The cats were discharged from the hospital the day after surgery and no problems were reported by the owners when phoned 1 week after surgery.

Discussion

To the author's knowledge this is the first study describing the cardiorespiratory effects of alfaxalone in cats and comparing it to propofol for induction and maintenance. We observed higher SpO_2 levels, less hypercapnia and a lower necessity for ventilatory support in the alfaxalone group. No difference in occurrence of apnoea was observed between groups.

Cardiovascular and ventilatory effects

In the present study, 80% of the cats receiving propofol required controlled ventilation *versus* only 20% of the alfaxalone group. This is similar to previous findings where the occurrence of apnoea was between 12.5 and 25% in cats receiving 5–15 mg kg^{-1} alfaxalone IV (Muir et al. 2009). It also supports the hypothesis that in cats alfaxalone has a broader therapeutic range leading to less observation of hypoventilation compared to propofol. Similarly, in a dose escalation study, dogs receiving propofol for induction were more prone to apnoea than alfaxalone-anaesthetised dogs (Keates & Whittem 2012). In contrast, similar levels of hypoventilation were observed comparing alfaxalone and propofol for induction and maintenance in dogs (Suarez et al. 2012).

The MAP (Fig. 2c) was higher over time in group P while no differences were seen in PR. This suggests that propofol has less negative inotropic or vasodilatative effects than alfaxalone. However, none of the cats displayed hypotension. This confirms a similar observation that cardiovascular variables remained stable during propofol anaesthesia in traumatised cats (Liehmann et al. 2006). In a study by Schwarz et al. (2014) premedication had a significant influence on arterial pressure using alfaxalone CRI for maintenance in healthy cats. Hypotension occurred in more than 50% of the cats premedicated with acepromazine, but in <10% after 20 µg kg^{-1} of medetomidine IM.

The statistically significant difference observed in SpO_2 is mainly due to the different effects of the two drugs on respiration and ventilation in the first 10 minutes after induction. In all six cats in group P the drop in SpO_2 < 90% was associated with hypoventilation or apnoea rather than changes in cardiovascular variables.

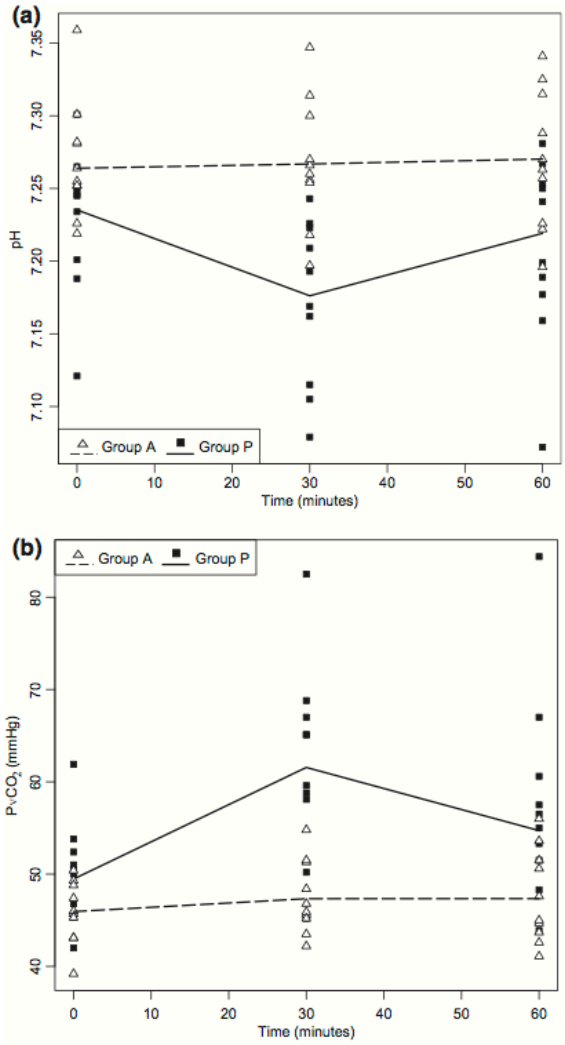

Figure 3 (a) Mean pH and (b) mean partial pressure of carbon dioxide in venous blood ($PvCO_2$, mmHg) over time in 20 cats under alfaxalone (group A) or propofol (group P) continuous rate infusion, premedicated with medetomidine and meloxicam.

When Figs 3a and b are considered together, it becomes obvious that the higher $PvCO_2$ level in group P caused the significant difference in pH between groups. The difference between the two groups for $PvCO_2$ [15 mmHg (2 kPa) 30 minutes after induction] was not statistically significant but might be clinically relevant. On the other hand, no difference was observed in $PE'CO_2$ values between group A and P. The use of side-stream capnography in small patients with a high respiratory rate and a shallow breathing pattern together with a non-rebreathing system may limit the interpretation of the $PE'CO_2$ in this study, because a relative dilution of the effectively expired carbon dioxide may occur, resulting in a false-low $PE'CO_2$ (Fretschner et al. 1992). The fresh gas flow, the monitoring system and the sample site were identical for all cats in both groups. However, the tidal volume in group P might have been lower than in group A because the $PvCO_2$ was higher 30 minutes after induction. The lower tidal volume might have caused some degree of dilution and a lower $PE'CO_2$. The stable BE and the small, although significant difference in HCO_3 rules out a metabolic influence on pH. The difference in Hb between groups was not considered to be clinically relevant.

Alfaxalone and propofol dose rates

The alfaxalone induction and CRI doses were chosen based on the summary of product characteristics (SPC) drug sheet and recommendation from previously published data (Muir et al. 2009; Schwarz et al. 2014). The propofol induction dose is based on one study comparing propofol and alfaxalone induction in cats (Martinez Taboada & Murison 2010). Propofol CRI doses were based on published data in cats for clinical use (Liehmann et al. 2006).

The high induction doses of 11.6 ± 0.3 and 11.7 ± 2.7 mg kg^{-1} in group A and P were unexpected especially after premedication with medetomidine. In other studies induction doses ranged between 1 and 7 mg kg^{-1} for alfaxalone and 2–12 mg kg^{-1} for propofol (Martinez Taboada & Murison 2010; Mathis et al. 2012). One possible explanation for the high mean induction doses in the present study is the difference in the premedication used. While in the aforementioned studies acepromazine (0.05 mg kg^{-1} IM) was used as premedication, we used an α_2-agonist, namely medetomidine (0.01 mg kg^{-1} IM). Recently it has been shown that dexmedetomidine (0.01 mg kg^{-1} IM) increases the blood circulatory time compared to acepromazine (0.04 mg kg^{-1} IM) and methadone (0.2 mg kg^{-1} IM) premedication in dogs (Rocchi et al. 2013). The slower circulation prolongs the time period until the peripherally administered drug reaches an anaesthetic level in the brain. Therefore a relative overdosage of an induction agent is more likely to occur when using an α_2-agonist.

A second explanation for the higher induction doses is the method of drug administration. Continuous administration of the agents using a syringe driver was used to overcome any human variability. The fact that there was no break in the administration of the drug to assess its early effects could have led to a possible overdose.

Table 2 Comparison of recovery times between cats anaesthetized with alfaxalone (group A) or propofol (group P) as continuous rate infusions, after premedication with medetomidine and meloxicam

	Group A			Group P			
	n	Mean	±SD	*n*	Mean	±SD	*p* value
Head lift* (minutes)	8	72	37	6	49	15	0.19
Sternal position† (minutes)	6	78	45	6	57	17	0.30

n = as indicated. *Defined as time from end of CRI to first controlled attempt to lift the head. †Defined as time from end of CRI to first controlled sternal position of the cat.

After reviewing the anaesthetic records, there was no obvious reason for the high requirement of 0.5 mg kg^{-1} boli in the two cats per group. However, an inadequate plane of anaesthesia was noted in some of the cats. Purposeful movements might have been an indication for inadequate hypnosis or analgesia. It can be assumed that alfaxalone and propofol as single agents for maintenance of anaesthesia for major surgical procedures may not prevent haemodynamic responses or purposeful movements to noxious stimulation unless a large dose to produce deep anaesthesia is employed resulting in major cardiorespiratory depression. Applying a multimodal analgesia regime during maintenance would improve quality and avoid signs of light plane of anaesthesia.

Premedication and analgesia

Results of preliminary trials indicated a satisfactory level of sedation when using medetomidine 0.01 mg kg^{-1} IM and adequate analgesia if combined with meloxicam 0.3 mg kg^{-1} SC. We decided to use medetomidine despite its potential influence on the respiratory rate (Bergström 1988) due to its wide clinical use in cats and its analgesic effects (Slingsby et al. 1998; Ansah et al. 2002). All possible stress to the cats was avoided after premedication and before anaesthesia. This resulted in the same sedation score directly before inducing anaesthesia in both groups.

No opioid was administered before or during anaesthesia to exclude their potential depressive influence on the respiratory center (Lalley 2003). The administration of a non steroidal anti-inflammatory drug pre-emptively might have obscured potential episodes of apnoea and hypoventilation due to a reduction in requirements of anaesthetic drugs as described in dogs (Yamashita et al. 2008). However, performing the study without the administration of any analgesic drug would have been inacceptable ethically.

Limitations and future studies

The decision to administer the induction agent with a syringe driver and at a relatively fast rate might have influenced the induction doses observed in the present study. The drug administration using a syringe driver aimed to avoid any influence by inconsistent manual injection of either drug. In future studies, alfaxalone and propofol induction doses and quality of induction in cats could be determined using slower infusion rates.

Evaluation of arterial blood gases in a larger group of cats might show more accurately the influence of the two anaesthetic agents on gas exchange compared to the monitoring methods ($P_E'CO_2$, $PvCO_2$, SpO_2) used in our clinical study. A mainstream capnograph in combination with a circle breathing system, could also have improved the accuracy of the measured $P_E'CO_2$ in relation to the $PvCO_2$.

Future studies using invasive cardiovascular monitoring including cardiac output and systemic vascular resistance measurements should elucidate the effect of the two drugs on the central and peripheral cardiovascular system.

Conclusion

We conclude that both alfaxalone and propofol are suitable for induction and maintenance of anaesthesia in cats, but alfaxalone has less adverse influence on respiration than propofol. Alfaxalone might be the preferable drug to induce and maintain anaesthesia in cats when no possibility for controlled ventilation is available.

Acknowledgements

We would like to thank Dr. Fraser Lewis and Dr. Sonja Hartnack for statistical consultation.

Conflict of interests

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

References

Andress JL, Day TK, Day DG (1995) The effects of consecutive day propofol anesthesia on feline red blood cells. Vet Surg 24, 277–282.

Ansah OB, Vainio O, Hellsten C et al. (2002) Postoperative pain control in cats: clinical trials with medetomidine and butorphanol. Vet Surg 31, 99–103.

Bergström K (1988) Cardiovascular and pulmonary effects of a new sedative/analgesic (medetomidine) as a preanaesthetic drug in the dog. Acta Vet Scand 29, 109–116.

Beths T, Touzot-Jourde G, Musk G et al. (2014) Clinical evaluation of alfaxalone to induce and maintain anaesthesia in cats undergoing neutering procedures. J Feline Med Surg 16, 609–615.

Fretschner R, Warth H, Deusch H et al. (1992) Capnometry in pediatric anesthesia. The effect of the measurement site and respiratory rate. Anaesthesist 41, 463–467.

Keates H, Whittem T (2012) Effect of intravenous dose escalation with alfaxalone and propofol on occurrence of apnoea in the dog. Res Vet Sci 93, 904–906.

Lalley PM (2003) μ-Opioid receptor agonist effects on medullary respiratory neurons in the cat: evidence for involvement in certain types of ventilatory disturbances. Am J Physiol Regul Integr Comp Physiol 285, 1287–1304.

Liehmann L, Mosing M, Auer U (2006) A comparison of cardiorespiratory variables during isoflurane–fentanyl and propofol–fentanyl anaesthesia for surgery in injured cats. Vet Anaesth Analg 33, 158–168.

Martinez Taboada F, Murison PJ (2010) Induction of anaesthesia with alfaxalone or propofol before isoflurane maintenance in cats. Vet Rec 167, 85–89.

Mathis A, Pinelas R, Brodbelt DC et al. (2012) Comparison of quality of recovery from anaesthesia in cats induced with propofol or alfaxalone. Vet Anaesth Analg 39, 282–290.

Morgan DW, Legge K (1989) Clinical evaluation of propofol as an intravenous anaesthetic agent in cats and dogs. Vet Rec 124, 31–33.

Muir W, Lerche P, Wiese A et al. (2009) The cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in cats. Vet Anaesth Analg 36, 42–54.

Rocchi A, Ambrisko TD, Moens Y (2013) Effect of dexmedetomidine vs. acepromazine-methadone premedication on limb to lung circulation time in dogs. Vet J 195, 357–360.

Schwarz A, Kalchofner K, Palm J (2014) Minimum infusion rate of alfaxalone for total intravenous anaesthesia after sedation with acepromazine or medetomidine in cats undergoing ovariohysterectomy. Vet Anaesth Analg 41, 480–490.

Slingsby LS, Lane EC, Mears ER et al. (1998) Postoperative pain after ovariohysterectomy in the cat: a comparison of two anaesthetic regimens. Vet Rec 143, 589–590.

Suarez MA, Dzikiti BT, Stegmann FG et al. (2012) Comparison of alfaxalone and propofol administered as total intravenous anaesthesia for ovariohysterectomy in dogs. Vet Anaesth Analg 39, 236–244.

White PF (1983) Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology 59, 294–300.

Whittem T, Pasloske KS, Heit MC et al. (2008) The pharmacokinetics and pharmacodynamics of alfaxalone in cats after single and multiple intravenous administration of Alfaxan at clinical and supraclinical doses. J Vet Pharmacol Ther 31, 571–579.

Yamashita K, Okano Y, Yamashita M et al. (2008) Effects of carprofen and meloxicam with or without butorphanol on the minimum alveolar concentration of sevoflurane in dogs. J Vet Med Sci 70, 29–35.

Received 15 January 2014; accepted 24 June 2014.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Cardiovascular criteria for continuous rate infusion (CRI) dose rate adjustment (performed every 5 minutes) throughout anaesthesia in 20 cats under alfaxalone (group A) or propofol (group P) CRI, premedicated with medetomidine and meloxicam.

Danksagung

Auf diesem Weg der Wissenschaft und natürlich auf dem Papier auf welchem die Arbeit geschrieben wurde, möchte ich ein paar Worte an die, die mich immer gefördert haben richten.

Diese Dissertation möchte ich Ion, Helena, Elio und Giovanna, für die während meiner Studienjahre bedingungslose Unterstützung, widmen. Ich konnte jederzeit von einer konstanten Ermunterung, Rückhalt und Begeisterung profitieren. Sie haben immer an mich geglaubt, auch dann, wenn mein Charakter ihre Geduld auf die Probe gestellt hat.

Eine wissenschaftliche Arbeit ist nie das Werk einer einzelnen Person.
Deshalb möchte ich mich auch bei Frau Prof. Bettschart bedanken, speziell für die Art und Weise, wie Sie die Abteilung für Anästhesie leitet. Sie zeigt nicht nur stets eine ungeheure Leidenschaft für die Wissenschaft, sondern auch ein großes Herz, darum fühlen wir uns wie ein Teil von etwas Größerem, als “nur” ein Team von Anästhesisten.
Die unerschöpfliche und immer wieder verbreitete Energie die aus Frau Dr. Mosing entspringt hat diese Arbeit stark beeinflusst. Ihre wissenschaftliche Hinweise waren stets eine Bereicherung und jederzeit stand Sie für konstruktive Gespräche zur Verfügung.
Als überaus genaue und sorgfältige Zweitauthorin stand Frau Dr. Schwarz immer bereit, um mich auf den richtigen Weg zu leiten, wenn ich mich wieder in meinen Gedanken oder meinem Tun verloren hatte.

Ihnen Allen gilt mein besonderer Dank.

Lebenslauf

Name	Ivo Ulisse Campagna
Geburtsdatum	13.05.1983
Geburtsort	Lugano
Nationalität	Schweizer
Heimatort	Chironico (TI)

1995 – 1998	Scuola Media Massagno, Massagno, Schweiz
1998 – 2003	Liceo Lugano 2, Savosa, Schweiz
2003 – 2009	Studium Veterinärmedizin, Vetsuisse-Fakultät Universität Zürich, Zürich, Schweiz
September 2009	Staatsexamen, Eidg. Dipl. Tierarzt, med. vet., Vetsuisse-Fakultät Universität Zürich, Zürich, Schweiz
2011 – 2015	Anfertigung der Dissertation unter der Leitung von PD Dr. med. vet. Martina Mosing, dipl ECVAA, Abteilung für Anästhesiologie Departement für Pferde, Vetsuisse-Fakultät Universität Zürich, Schweiz, Direktor: Prof. Dr. med. vet. Anton Fürst
2011 – dato	Assistent, Abteilung für Anästhesiologie, Departement für Pferde, Vetsuisse-Fakultät Universität Zürich, Schweiz